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ORIGINAL ARTICLE

Are physical and mental abilities of older people related to gonadotropins and steroid hormones levels?

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Abstract

BACKGROUND: Aging is characterized by deep alterations of hormone secretion. In majority, hormone secretion, except gonadotropins, undergoes a pronounced decrease which is thought to contribute to the progression of aging. The recent data indicate that gonadotropin excess may also by itself influence the aging process. The aim of the present study was to investigate the relations between gonadotropins and steroid hormones with physical and mental abilities of older people.

MATERIAL AND METHODS: In a group of patients aged over 75 years, concentrations of FSH, LH, estradiol, testosterone, DHEAs and cortisol were measured. The mental ability was estimated by MMSE and CDT and the physical ability by TUG and SPPB tests.

RESULTS AND CONCLUSIONS: The positive correlation between SPPB scores and FSH and the negative correlations of SPPB with LH/FSH ratio were observed in men. The correlation of TUG scores and estradiol levels was also noted in men. The positive correlation between CDT scores and FSH in women and the negative correlation between CDT and LH/FSH ratio in men were found. The correlation between the results of CDT and cortisol levels in men was also observed. Thus, we did not confirm the simple deleterious effect of gonadotropins on cognitive abilities. FSH and LH seem exert different (antagonistic?) effects on cognitive functions, but this hypothesis needs further studies.

INTRODUCTION

Aging in humans, like in other mammalian species, is associated with deep alterations in hormonal secretion. In turn, these alterations, mostly hormone deficiencies, actively contribute to this process. A decrease of gonadal hormone secretion which occurs both in females and male (although in women these changes are more sharp than in men) is considered as a causal factor of many age-related disturbances, including the impairments of mental and physical abilities (for review see: Warren & Ng 2006; Medras & Karasek 2006). Since the adrenocortical steroid dehydroepiandrosterone (DHEA) secretion declines as a function of age, it was hypothesized that its deficiency may

contribute to accelerated aging (Pawlikowski & Karasek 2006, Klinge *et al.* 2018). The impairment of gonadal function leads in advanced age to a distinct increase of gonadotropin secretion, usually greater in women. However, in contrast to the role of gonadal hormones deficiency, which is considered as important, the possible roles of the excess of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the process of aging have been neglected for a long time. In 1994 one of the authors of the present paper proposed a hypothesis that the gonadotropin excess may also contribute to the aging process by the direct extra-gonadal action (Pawlikowski 1994). The further studies identified FSH and/or LH receptors in different organs and tissues. The more recent studies confirm the possibility of direct actions of gonadotropins beyond the reproductive system (for review see: Pawlikowski 2019). The FSH and/or LH receptors were identified in many organs, like the brain (Lei *et al.* 1993), adrenal cortex (Pabon *et al.* 1996; Lasley *et al.* 2016; Korol *et al.* 2019), brown adipose tissue (Liu *et al.* 2015; Liu et al 2017), osteoclasts and monocytes (Komorowski & Stepien 1994, Robinson *et al.* 2010). Recently, it was also suggested that high levels of LH could be involved in the impairment of the cognitive functions in older human subjects and in pathogenesis of Alzheimer's disease (Barron *et al.* 2006; Webber *et al.* 2007a; 2007b; Batha *et al.* 2018). Nevertheless, current literature lacks data on the relationship of circulating gonadotropins to physical and mental functioning in advanced age.

Therefore, the goal of the present study was to see whether physical and cognitive function in very old people (over 75 years) estimated by means of the respective tests depend on the steroid hormones and gonadotropin levels.

MATERIAL AND METHODS

Patients

The project was approved by the Bioethical Committee of the Medical University of Lodz, decision number RNN/363/17/KE. The study material comprised 100 volunteer outpatients of the Geriatric University Clinic, Central Veterans' Hospital in Lodz (Poland): 61 women (aged in the time of investigation 76-90 years; mean age: 80.61 yrs.) and 39 men (aged 76-88 years; mean age: 79.56 yrs.).

Laboratory measurements

The quantitative determinations of the following hormones levels in blood serum were performed: follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), testosterone, dehydroepiandrosterone sulfate (DHEAs) and cortisol. The blood samples were taken from the cubital vein in the morning. For determinations, we used the technology based on the competitive or sandwich chemiluminescence immunoassays (CLIA). Measurements were performed on the LIAISON XL analyzer from DiaSorin Inc. (Saluggia, VC, Italy or Stillwater, MN, USA) using the kits produced by this Company and dedicated to the this analyzer (Table I).

Physical and cognitive function measurements

The physical ability was measured by the Timed Up and Go (TUG) (Podsiadlo & Richardson 1991) and Short Physical Performance Battery (SPBB) (Guralnik *et al.* 1995) tests.

The mental ability was estimated by the Mini-Mental State Examination (MMSE) (Folstein *et al.* 1975) and Clock Drawing Test (CDT) (Sunderland *et al.* 1989).

Statistical analysis

The differences between mean values were evaluated by Student's t test and correlations of the numerical data by means of Spearman's test. The quantitative parameters were expressed as mean value ± standard deviation. Statistical significance was set at $p < 0.05$.

RESULTS

The results of hormone determinations have been shown in Table II. Their mutual correlations were described in previous paper (Pawlikowski *et al.* 2019). In this study we estimated their possible correlations with the numerical results of chosen tests of physical and mental abilities (Table III). As it can be seen there, the significant positive correlation between SPPB scores and FSH and the negative correlation of SPPB and LH/FSH ratio were observed in men. The positive (but weak) correlation between LH/FSH ratio and TUG results is also noticed in this sex. The latter observation corroborates with the former because in contrast to SPPB, the higher scores of TUG indicate the worse ability. In this gender, the significant correlation of TUG scores and E2 levels was also observed. When the cognitive ability tests were taken into consideration, the positive significant correlation between CDT scores and FSH in women and the negative correlation between CDT and LH/FSH ratio in men were found. The positive correlation between the results of CDT and cortisol levels in men was also observed (Table III).

DISCUSSION AND CONCLUSIONS

In the present study we assessed the relationship of gonadotropin levels to physical and mental abilities in subjects of very advanced age. Unlike some previous studies performed in younger populations, we did not confirm the deleterious effect of gonadotropins on physical and cognitive abilities. The decline in steroid gonadal hormones has been implicated in decreasing physical and mental functioning (Travison *et al.* 2011; Collins *et al.* 2019). Recent emerging data indicates that not only gonadal hormones but also gonadotropins may exert direct action in different tissues (see Introduction).

Tab. 1. The expected values and precisions of the assays with LIAISON XL analyzer

Test	Expected values for women	Expected values for men	Repeatability (within-assay variability) [%]	Reproducibility (between-assay variability) [%]
FSH (REF 312251)	13.9-103.1 mIU/mL post-menopausal	1.3-11.8 IU/mL	2.3-5.6	2.9-4.8
LH (REF 312201)	15.4-53.3 mIU/mL post-menopausal	2.8-6.8 mIU/mL	2.8-6.8	3.1-9.0
Estradiol II Gen. (REF 310680)	<36.7-241.1 pmol/L post-menopausal	38.9-163.3 pmol/L	2.1-3.9	4.2-10.7
Testosterone (REF 310410)	0.27-1.76 nmol/L ≥ 50 years	≥ 50 years 6.76-31.05 nmol/L	2.8-7.3	7.1-14.0
DHEAs (REF 310430)	> 60 years 61.6-124.1 µg/dL	> 60 years 40.8-405.4 µg/dL	3.99-7.09	5.31-8.97
Cortisol (REF 313261)	4.5-24.0 µg/dL	4.5-24.0 µg/dL	3.5-4.9	3.2-7.1

Elevated serum FSH has been suggested to play a role in bone loss, obesity, cardiovascular and cancer risk (Pawlikowski 2019; Lizneva *et al.* 2019). In men treated for prostate cancer with androgen deprivation therapy (ADT), FSH has been suggested to increase the risk of atherosclerosis, insulin resistance, metabolic syndrome and increased bone resorption (Crawford *et al.* 2017). Metformin, a well-known drug improving the insulin resistance, was shown to decrease FSH levels (and to less degree LH levels) in the postmenopausal women suffering from type 2 diabetes (Krysiak *et al.* 2018). In the European Male Aging Study higher levels of frailty index were significantly associated with lower levels of total and free testosterone, DHEAs and higher levels of gonadotropins and SHBG (Tajar *et al.* 2011). In the present study we observed some relationships of physical ability tests (SPPB and TUG) with hormone levels in the men. However, except the possible link between lower DHEAs levels and poorer SPPB scores their significance is difficult to explain. Better function (higher SPPB) with increasing FSH in older men may seems contradictory with available data; however, several points should be considered. In very advanced age, the associations observed in younger subjects may be different. For example, in the European Male Ageing Study, higher LH and FSH were positively related to worsening frailty index only in men < 60 years (Swiecicka *et al.* 2018). In advanced age, the deleterious impact of FSH promoting fat-building and metabolic diseases may be viewed in different way. To protect function the most important task in advanced age is to preserve lean body mass loss. However, lean mass and fat mass are closely correlated. For example, in postmenopausal women, FSH was inversely correlated both with lean and fat mass (Gurlay *et al.* 2012). Similarly, in urban African women FSH correlated negatively with total lean mass (Jaff *et al.* 2015). In our previous paper we also showed the negative correlation of FSH with body mass indices in the older (over 75 years old) women (Pawlikowski *et al.* 2019). Likewise, higher TUG (lower function) association with estradiol in men may reflect higher age-related gonadotropin levels. Taken together those data might suggest that gonadotropins may be markers of declining function and frailty with ageing; however, with unclear pathogenic role at this point. Observed for the first time direct relationship of FSH to SPBB merits further investigations. The negative effects of gonadotropins, mostly of LH on cognitive function, were reported in many previous studies. LH levels were found to be higher in patients suffering from Alzheimer's disease (AD) in comparison to non-AD subjects and considered as a risk factor of AD (Barron *et al.* 2006; Webber *et al.* 2007a; 2007b; Batha *et al.* 2018). In animal studies LH leads to the accumulation of beta-amyloid protein, characteristic for AD, in brain (Verdile *et al.* 2015). Since the mammalian brain contains the LH receptors, a direct deleterious effect of LH on neuronal structures was hypothesized (Lei *et al.* 1993). Gonadotropins have been suggested to play a role in the production of amyloid-beta protein, and have been found to be more elevated in some

Tab. 2. Hormone levels for women (W) and men (M)

	FSH [mIU/mL]	LH [mIU/mL]	LH/FSH	estradiol [pmol/L]	testosterone [nmol/L]	DHEAs [µg/dL]	cortisol [µg/dL]
W	87.9±27.17	21.2±7.53	0.25±0.07	56.5±18.88	0.79±0.43	42.5±28.84	14.9±7.35
M	23.3±24.40	8.3±7.01	0.44±0.19	113.6±36.79	12.1±5.41	58.2±36.27	17.3±5.76

Tab. 3. Spearman correlation between tests (TUG, SPPB, MMSE, CDT) and hormone levels for women (W) and men (M)

Test\ hormone		FSH	LH	LH/FSH	estradiol	testosterone	DHEAs	cortisol
TUG	W	ns	ns	ns	ns	ns	ns	ns
	M	ns	ns	rho= +0.29 $p>0.05$	rho= +0.32 $p<0.05$	ns	ns	ns
SPPB	W	ns	ns	ns	ns	ns	ns	ns
	M	rho= +0.32 $p<0.05$	ns	rho= -0.34 $p<0.05$	ns	ns	ns	ns
MMSE	W	ns	ns	ns	ns	ns	ns	ns
	M	ns	ns	ns	ns	ns	ns	ns
CDT	W	rho= +0.30 $p<0.05$	ns	ns	ns	ns	ns	ns
	M	ns	ns	rho= -0.46 $p<0.05$	ns	ns	ns	rho= +0.38 $p<0.05$

patients with Alzheimer disease (Short *et al.* 2001). In a cross-sectional study in 282 postmenopausal women in Jakarta, FSH levels along with the ratio of FSH/estradiol levels significantly correlated with mild cognitive impairment (MCI) incidence (Hestiantoro *et al.* 2017). Blood concentrations of FSH and LH were significantly higher in 40 male residents of long-term care facilities with the primary diagnosis of dementia as compared to 29 age-matched controls (Bowen *et al.* 2000). In contrast, no difference in average LH and FSH levels between 45 men with Alzheimer disease cases and 133 older controls was found (Hogervorst *et al.* 2003). Higher estradiol levels were associated with better cognitive function both in perimenopausal and postmenopausal women but levels of FSH were unrelated to cognitive performance (Hu *et al.* 2017). In our study we noticed a positive correlation between CDT scores and FSH levels in women. No relationship of cognitive function tests to LH and to FSH in men was found. In 649 community-dwelling, non-demented older women residing in Western Australia, high LH levels were associated with a lower cognitive score in older women, but disproportionately well preserved cognitive functioning was found for the oldest women who had high levels of FSH (Rodrigues *et al.* 2008). Those findings indicate that FSH and LH may act in a different way on cognitive functioning. For these reasons we estimated in our study also correlations of LH/FSH ratio with the numerical results of the investigated tests. The pathophysiological significance of LH/FSH ratio is still poorly recognized. It is considered as a diagnostic indicator of polycystic ovary syndrome (PCOS) (Saucedo *et al.* 2016). Interestingly, it is negatively correlated with the activity of brain regions responsible for visuospatial working memory in the patients with PCOS (Lai *et al.* 2019). Our finding that LH/FSH ratio correlate negatively with the indicators of physical and mental abilities in older men seems interesting and may be connected with a possible antagonistic activity of both gonadotropins. However, the hypothesis in question needs further studies to be approved. On the other hand, we noticed the positive correlation between cortisol levels and CDT scores in the men. The interpretation of this finding is difficult. In contrast to gonadal steroid hormones and DHEA, the secretion of cortisol is not diminished during aging and its role in the process of aging is considered rather as deleterious (Carlson *et al.* 1999; Ouanes & Popp 2019). A decrease of DHEAs blood levels is suggested as implicated in age-associated cognitive decline (Carlson *et al.* 1999; Ouanes & Popp 2019; Davis *et al.* 2008; Sorwell & Urbanski 2010). The link between E2 levels and estrogen replacement therapy with cognition is also reported (Sherwin 2007). Therefore, this finding may not be accidental. Although performed in rather unique population of advanced-age subjects, the present study has several shortcomings. Our subjects were physically and cognitively fit enough to volunteer and to present to the clinic for multiple measurements. None of our patients was diagnosed with AD or severe dementia. The vast majority of our patients presented a satisfactory scores of physical and mental tests. Thus, we cannot exclude the different effects of gonadotropins on cognitive function in other populations of older persons, as well as in different cultures and settings. Independently of some difficulties of interpretation, our data indicate that gonadotropins via their direct action influence the physical and mental abilities during aging. Potential sex-related dissimilarities in gonadotropin activities as well as differences between LH and FSH need further studies.

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